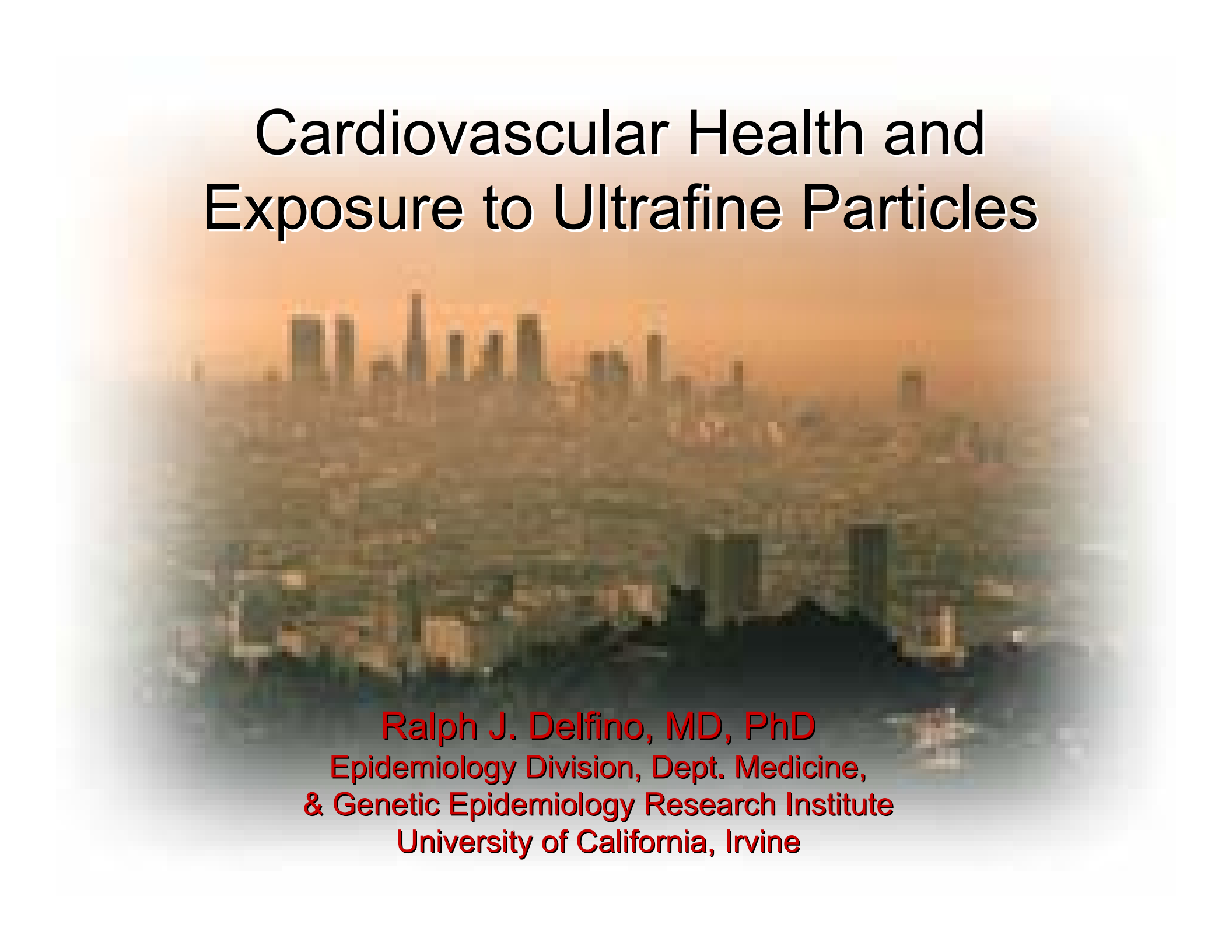
Cardiovascular Health and Exposure to Ultrafine Particles



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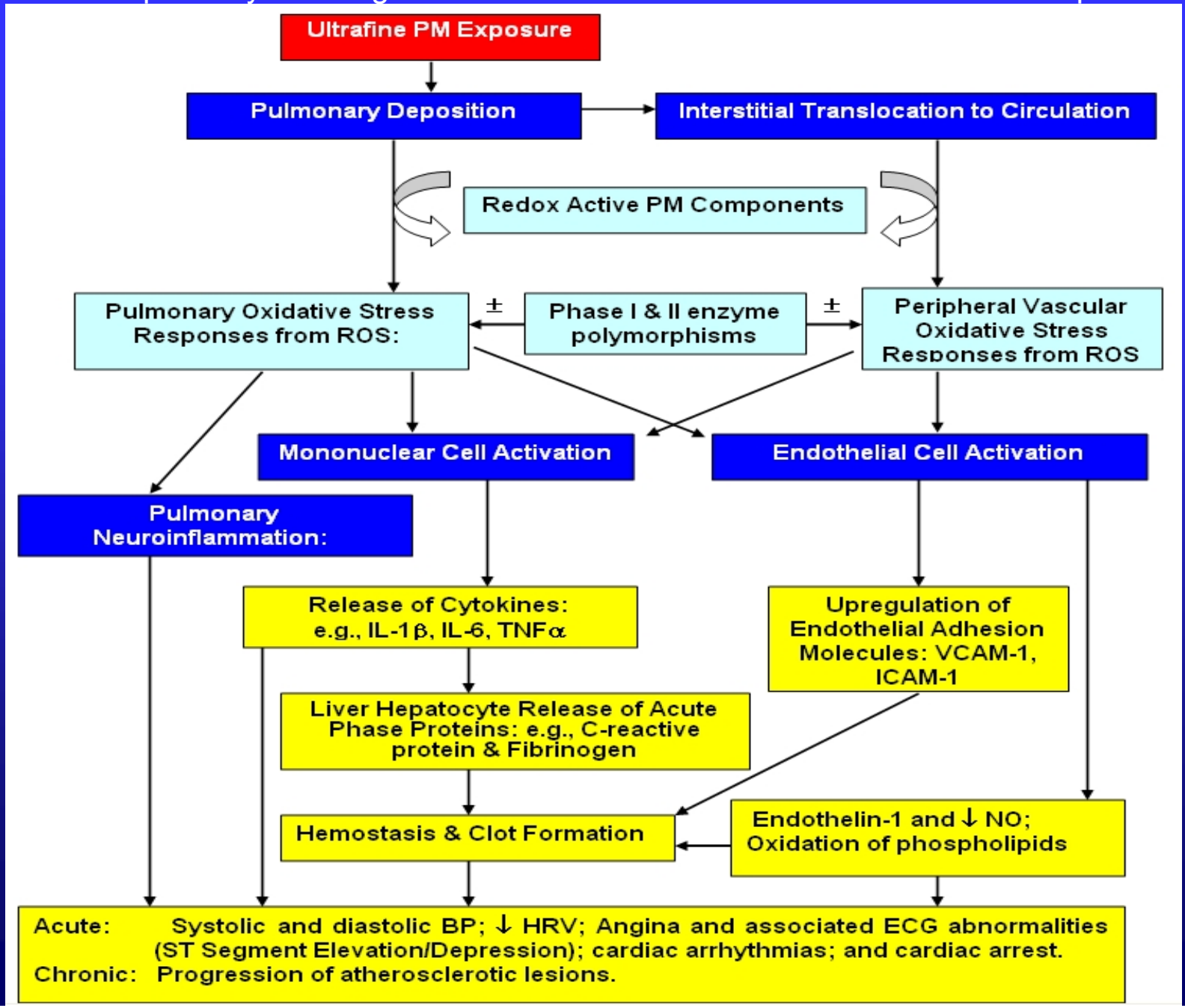
Ultrafine PM characteristics

- magnitudes higher particle number concentration & surface area than larger particles;
- can carry large amounts of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds & transition metals) having pro-inflammatory effects, partly a result of ROS;
- high pulmonary deposition efficiency;
- translocates into the pulmonary interstitium & then systemically → vascular endothelium.

Hypothesized pathways leading to adverse cardiovascular health effects from exposure to UFP



Background: Time Series Studies

- Daily ambient PM_{10} & $PM_{2.5}$ mass concentrations have been associated with cardiovascular hospital admissions & mortality:
  - National Morbidity, Mortality and Air Pollution Study in 90 U.S. cities.
  - 14 U.S. cities: PM_{10} from mobile source emissions & oil combustion (EPA estimates) showed the strongest associations with cardiovascular admissions vs. fugitive dust (coarse PM), wood burning, coal.

Background: American Cancer Society Cohort Study

- 319,000-500,000 subjects, 16 years follow-up across all U.S. urban areas.
- 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with 8-18% increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest.

Pope et al. 2004; Circulation 109:71-77

Netherlands Cohort Study on Diet and Cancer

- 5,000 persons with 8 years follow-up
- Cardiopulmonary mortality was associated with indicators of traffic-related air pollutants:
  - living near high traffic density, RR 1.95 (95% CI: 1.09, 3.52)
  - 10 $\mu g/m^3$ black smoke from background + local (proximity to streets), RR 1.71 (95% CI: 1.10, 2.67)
  - 30 $\mu g/m^3$ background + local NO_2, RR 1.81 (95% CI: 0.98, 3.34).

Hoek et al. 2002

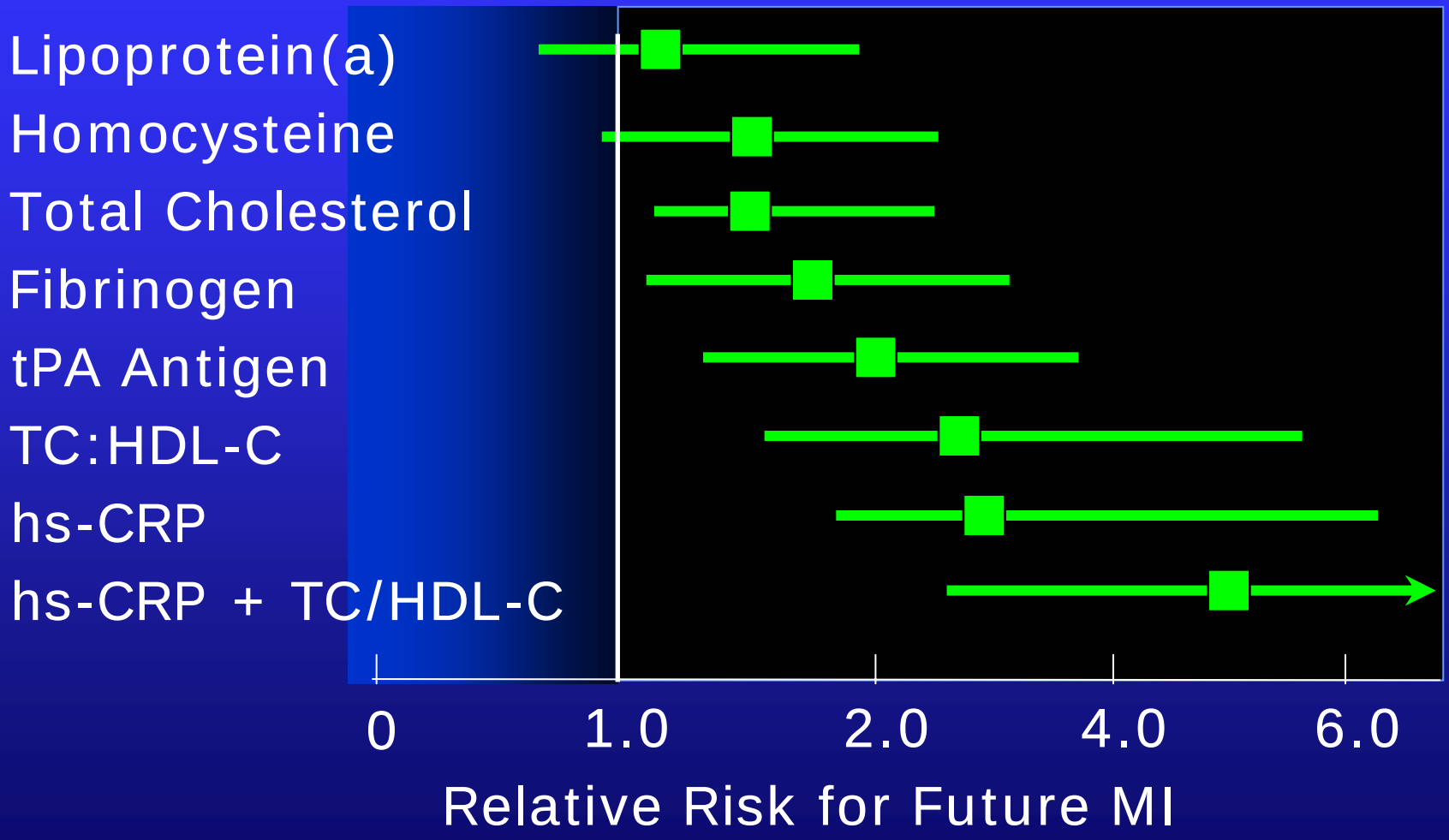
Peters et al. 2004 NEJM 351:1721-30

- Case-crossover study of 691 cases of MI, Augsburg Registry, subjects surviving at least 24h completed a time-activity diary.
- Positive association between reported exposure to traffic and onset of MI one hr later: OR = 2.92 (95% CI: 2.22, 3.83), $p < 0.001$.
- Little change after adjusting for exercise.
- Most common exposure was in a car, but associations were also found with public transport.

What is driving M&M associations?

- Causal pollutant components and sources?
- Biological mechanisms?
  - Autonomic dysfunction: ↓HRV, arrhythmias
  - ↑Inflammation & coagulation/thrombosis
  - Endothelial dysfunction: vasoconstriction (↓NO / ↑ET-1), upregulation of adhesion molecules.

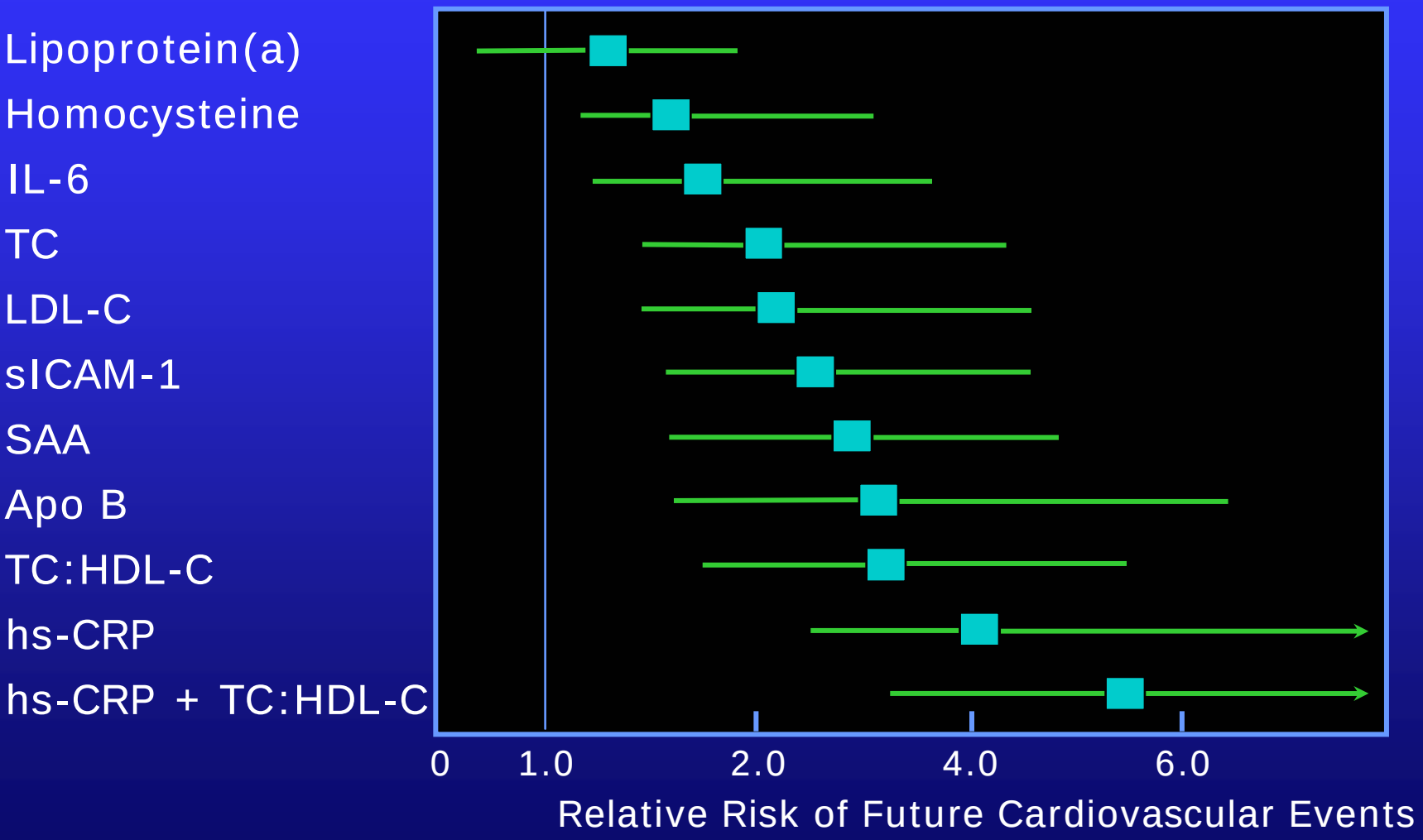
Relative Risks of Future MI among Apparently Healthy Middle-Aged Men: *Physician's Health Study*



Ridker PM. *Ann Intern Med* 1999;130:933-937.

Risk Factors for Future Cardiovascular Events: *WHS*

Ridker PM et al. *N Engl J Med* 2000;342:836-843.

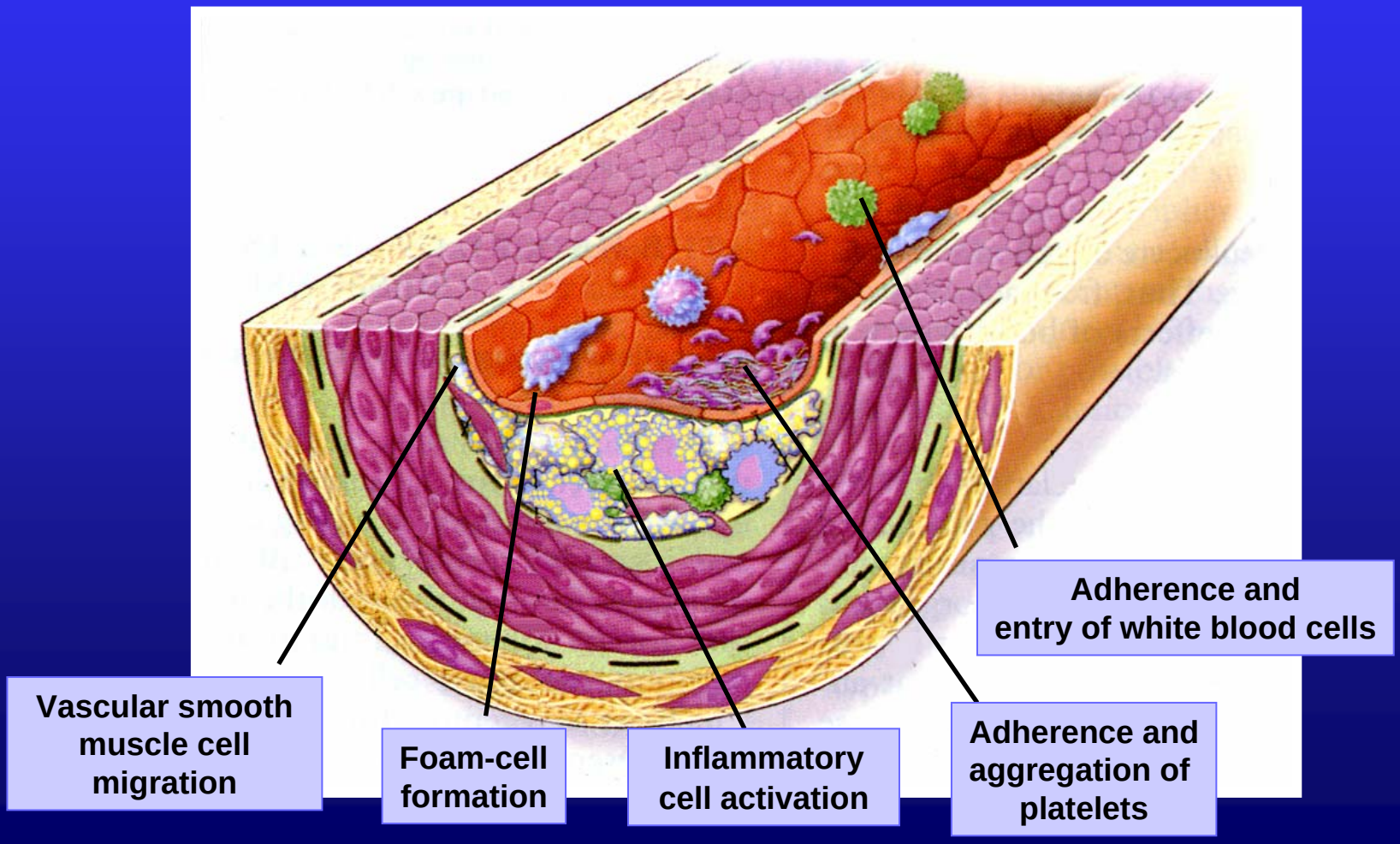


PM, Systemic Inflammation & Thrombosis

- Inflammation/endothelial dysfunction may determine plaque stability in CHD:
  - Unstable plaques have increased leukocytic infiltrates
  - T cells, macrophages predominate rupture sites
  - Cytokines and metalloproteinases influence both stability and degradation of the fibrous cap
- PM exposures have been associated with systemic hypercoagulability & inflammation:
  - increased cytokines, acute phase proteins and plasma viscosity.
  - major mechanism: PM-induced oxidative stress.

PM-induced oxidative stress

- ROS from PM → endothelial dysfunction and subsequent acute changes leading to plaque instability and rupture.
- Chronic changes -- atherosclerosis.



Epidemiologic evidence from acute exposure-response relationships

- Panel Studies, within-individual studies → evidence for possible pathophysiological mechanisms underlying the findings of epidemiologic time series.
- Outdoor fixed site PM exposures have been associated with:
  - systemic hypercoagulability & inflammation: increased cytokines, acute phase proteins and plasma viscosity.
  - decreased heart rate variability (HRV), increased blood pressure, cardiac arrhythmia and ST segment depression during exercise.

Peters et al. 2000 Epidemiol 11:11-17

- 100 subjects in eastern Massachusetts with implanted defibrillators (63,628 person-days of follow-up), ambient air pollution only.
- Defibrillator discharge interventions for ventricular tachycardias or fibrillation (33 subjects) associated with:
  - 26-ppb increase in NO_2 lagged 1 d, OR 1.8; 95% CI: 1.1, 2.9
  - black carbon & $PM_{2.5}$ confounded by NO_2

Pekkanen et al. 2002 Circulation 106:933-938

- Ambient PM, NO_2, CO exposure and ischemia during submaximal exercise tests in 45 subjects with CHD in Helsinki, Finland
- Significant three times increased risk for ST depression:
  - 1000 particles/cm^3 $NC_{0.1\text{-}1}$,
  - 10,000 particles/cm^3 $NC_{0.1}$. Independent of
  - 10 µg/m^3 $PM_{2.5}$
  - NO_2 and CO were also associated.

Riediker et al. 2004 Am J Respir Crit Care Med 169:934-940

- In-vehicle study of 9 healthy male North Carolina Highway Patrol troopers.
- In-vehicle 10 $\mu g/m^3$ $PM_{2.5}$ increase was associated with:
  - decreased lymphocytes (–11%, $p = 0.03$),
  - increased red blood cell indices (1%, $p = 0.03$),
  - increased neutrophils (6%, $p = 0.04$),
  - increased CRP (32%, $p = 0.02$), and
  - increased von Willebrand factor (12%, $p = 0.02$)
- NO_2 and CO were not significant

Chan et al. 2004 EHP 112:1063-1067

- personal exposure to PN (TSI P-TRAK) and HRV over one 16-hr daytime period in 9 young healthy adults and 10 older subjects with lung function impairments.
- Personal exposure to UFP NC was associated with decreased time-domain and frequency-domain HRV.

Ibald-Mulli et al. 2004 (ULTRA study) EHP 112:369-377

- Subjects with CAD, 37 in Amsterdam, 47 in Erfurt 47 in Helsinki, in-clinic BP biweekly over 6 mo, single-site ambient PM.
- small decrease in systolic BP ~(0.72 mm Hg) and diastolic BP ~(0.70 mm Hg) associated with a 5-day mean 10,000 UFP particles/cm^3.
- slightly stronger and more significant for 1,000 particles/cm^3 $PM_{0.1-1.0}$
- smaller associations were found for 10 $\mu g/m^3$ $PM_{2.5}$ mass.
- contrasts Zanobetti et al. (2004): ambient 5-d average $PM_{2.5}$ was positively associated with BP among 62 patients with pre-existing heart disease

Timonen et al. 2005 (ULTRA study) JEAEE in press online

- Same subjects as Ibald-Mulli 2004, in-clinic HRV biweekly over 6 mo, single-site ambient PM
- 10,000 particles/cm^3 UFP NC lag 2 was associated with changes in sympathetic/vagal tone:
  - 13.5 % decreased LF/HF
  - 2.9% increased HF/ (LF+HF)
- UFP associations were consistent across each city.
- $PM_{2.5}$ was associated with LF/HF HRV only in Helsinki (6% decrease), HF/(LF+HF) only in Erfurt (1.3 % increase), and HF in Helsinki (14% decrease).

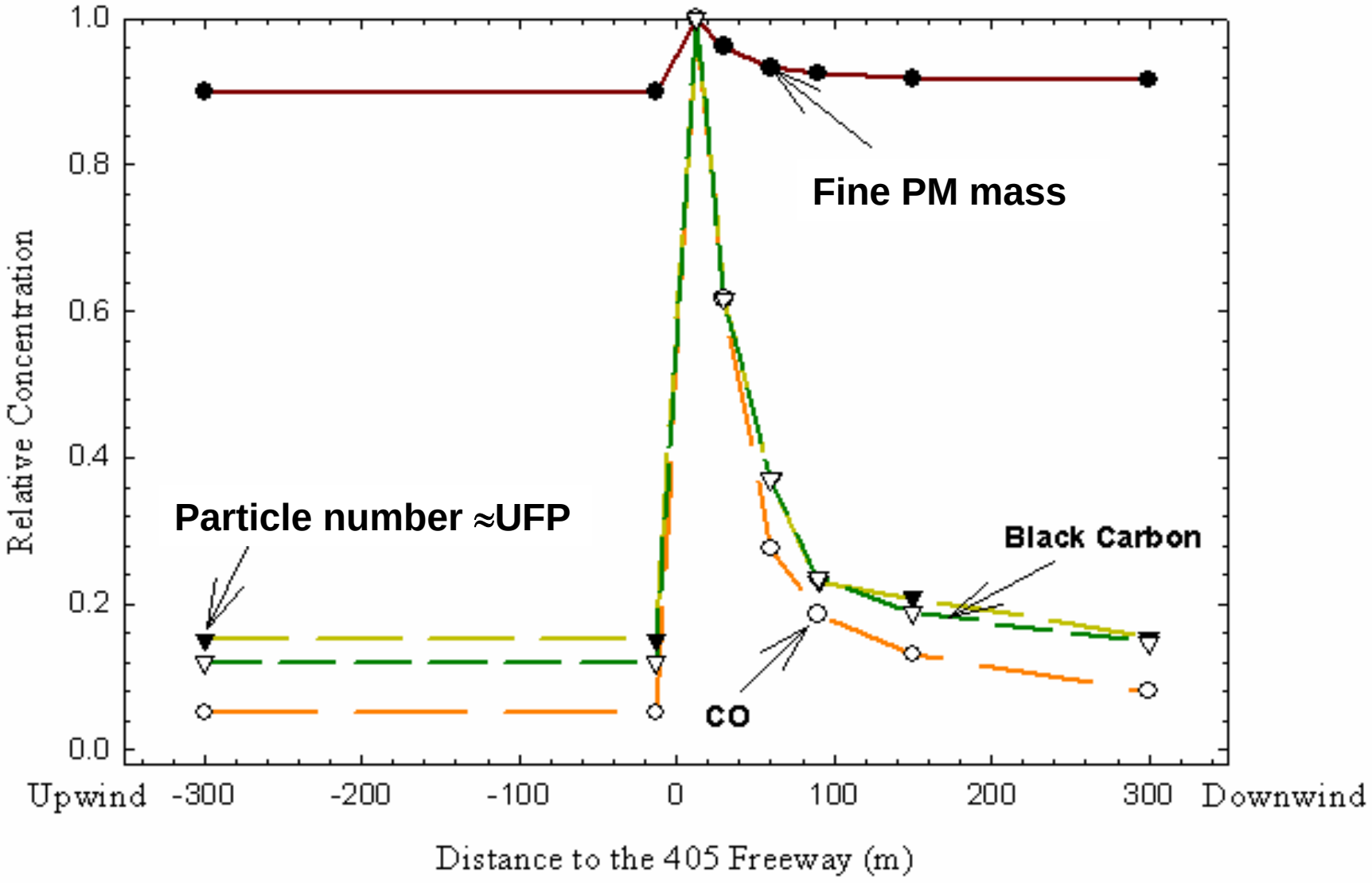
Ruckerl et al. 2005 Am J Resp Crit Care Med 173:432-441

- Erfurt panel of 57 males with CAD – blood draws in clinic 12 times, every 2 weeks, in winter
- All ambient PM size fractions were similarly associated with:
  - Increased CRP (inflammation)
  - Increased ICAM-1 and vWf (endothelial dysfunction)
  - Increased prothrombin fragment 1+2, (coagulation) but not D-dimer, and Factor VII decreased
- EC & OC associated with all outcomes except CRP
- Similar associations for CO and NO_2

State of Knowledge is Limited by Exposure Data

- EPA regulates PM mass $\rightarrow$ focus of epi. research;
- Regulatory focus on toxic PM components is weak;
- Data on UFP toxicity by source is needed;
- UFP high spatial variability / proximity to sources;
- Identifying traffic-related sources of PM toxicity is relevant as it is likely the predominant UFP exposure.

Ultrafine vs. fine PM Spatial Distribution



Zhu et al. J Air Waste Manage Assoc 52:1032-1042.

Unanswered Questions

- impact of UFP exposure on the CV health of a susceptible populations: elderly, subjects with CV disease, diabetes, COPD, etc:
  - Long-term progression of atherosclerosis by repeated acute impacts on systemic inflammation / ox stress and thrombosis?;
  - Acute risks (e.g., MI, stroke) posed by effects on cardiovascular autonomic function?
- importance of UFP composition and related source characteristics to cardiovascular and inflammatory outcomes
  (toxicity? reactive oxygen species? primary vs. secondary?)

Causal pollutant components?

- Problems with exposure data:
  - exposure misclassification due to reliance on pollutant data measured at central regional sites;
  - Reliance on PM mass alone: components can vary independently over space & time.
- Solutions proposed:
  - Personal and microenvironmental PM exposures;
  - Measurement of UFP mass & particle number conc.;
  - Assessment of PM sources & components using tracer compounds and surrogates (e.g., EC + traffic proximity and in-vehicle assessment).


Thank-you